Effects of positive pressure ventilation on extrathoracic organ systems

By Alex Yartsev - 15/06/2015
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This chapter is most closely associated with the demands of Section F10(i) of the 2023 CICM Primary Syllabus, which expects the trainees to *"describe the physiological consequences of intermittent positive pressure ventilation and positive end-expiratory pressure"*. Even if the college had ever asked any questions about this in the exams (which they haven't), the focus would usually be on the intrathoracic organs most immediately squished by the added pressure, them being the heart and lungs. The changes in the function of these systems have a tendency to overwhelm the discussion of the effects of positive pressure ventilation. However, one also needs to acknowledge that mechanical ventilation has effects on multiple other organ systems. These effects are generally closely tied to the systemic haemodynamic effects of positive pressure ventilation and the neurohormonal responses to them, which renders the authors' constant references to the "extrathoracic effects" of positive pressure ventilation increasingly inaccurate and ridiculous. Compounding the matter further, the chapter digresses extensively into some intrathoracic matters (such as the lymphatic drainage of the lungs), but for some reason not into others. What of the thymus? Perfusion of the spinal cord? What are the effects of positive pressure ventilation on the massive retrosternal goitre, and where would be an appropriate place for that discussion? Further digressions into that territory would be fruitless and wasteful of the exam candidates' precious time. The author is not oblivious to the reader's annoyance arising from these abuses but is indifferent to it.

In summary, the non-cardiopulmonary effects of positive pressure ventilation include:

- Raised intracranial pressure, if the PEEP is very high
- Water retention due to increased ADH release and aldosterone secretion
- Sodium retention due to decreased ANP release and aldosterone secretion

- Decreased renal perfusion and GFR (due to decreased cardiac output and increased renal venous pressure)
- Decreased hepatic perfusion and thus decreased metabolic clearance of drugs
- Decreased splanchnic perfusion, resulting id decreased intestinal motility and poor gastric emptying
- Decreased gastric perfusion, increasing the risk of stress ulceration
- Neutrophil retention in the pulmonary capillaries
- Impaired lymphatic drainage from the lungs

It is important to discriminate the effects of positive pressure ventilation from the effects of *mechanical ventilation*, which includes a large spectrum of additional interventions (sedation, paralysis, immobility, oral hygiene, intubation). This is a chapter specifically dealing with the effects of periodically insufflating a patient's lungs with pressurised gas.

There is little literature out there for this specific topic. One can find any number of review articles about the haemodynamic effects of PEEP but there is nothing to discuss the non-cardiac and non-pulmonary consequences of positive pressure ventilation. Solitary articles are scattered throughout the journals, each with a focus on some narrow aspect of this matter, but there is no single overarching review to which one might point the reader as a single definitive source.

Effects of positive pressure ventilation on intracranial pressure

It is a widely believed fact that a high PEEP (or positive pressure ventilation in general) gives rise to a raised intracranial pressure, particularly in brain-injured patients. The mechanism, when it is discussed, is generally thought to be obstruction of venous return – by impeding venous outflow from the brain, PEEP should decrease the perfusion gradient and therefore result in decreased cerebral blood flow. Theoretically, this makes sense, because cerebral perfusion pressure (CPP) is MAP minus either ICP or CVP, whichever is highest- and CVP is known to increase with positive pressure ventilation. However, experimentally the assertion that ICP or CPP (or CBF) are affected by PEEP rests on a fairly shaky foundation. With conflicting opinions from multiple existing studies, The Brain Trauma Foundation Guidelines (4th ed.) wisely do not mention PEEP at all. So, what is the trainee to say, when posed with the

question *"how does positive pressure ventilation influence intracranial pressure?"*

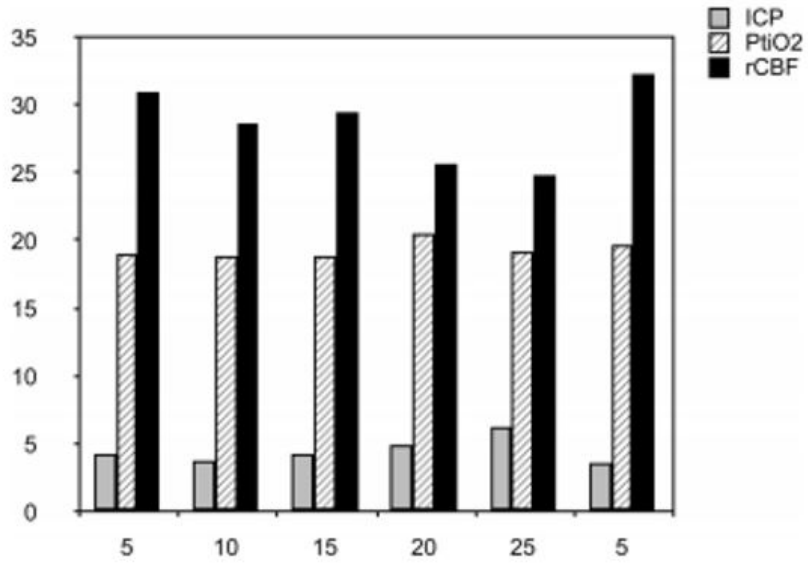
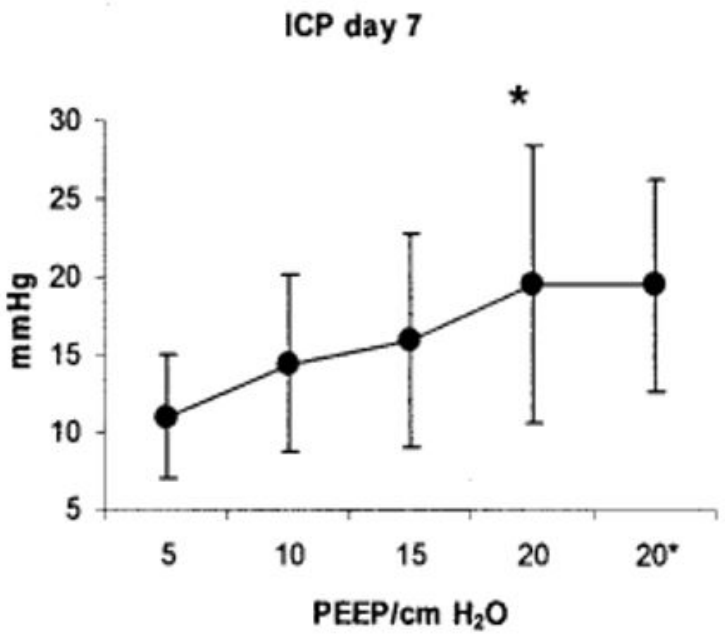


Figure 1. Effects of positive end-expiratory pressure (*PEEP*) on intracranial pressure (*ICP*), brain tissue oxygen tension ($Ptio_2$), and regional cerebral blood flow (rCBF) in healthy pigs. Data are expressed as mean values ± SD.

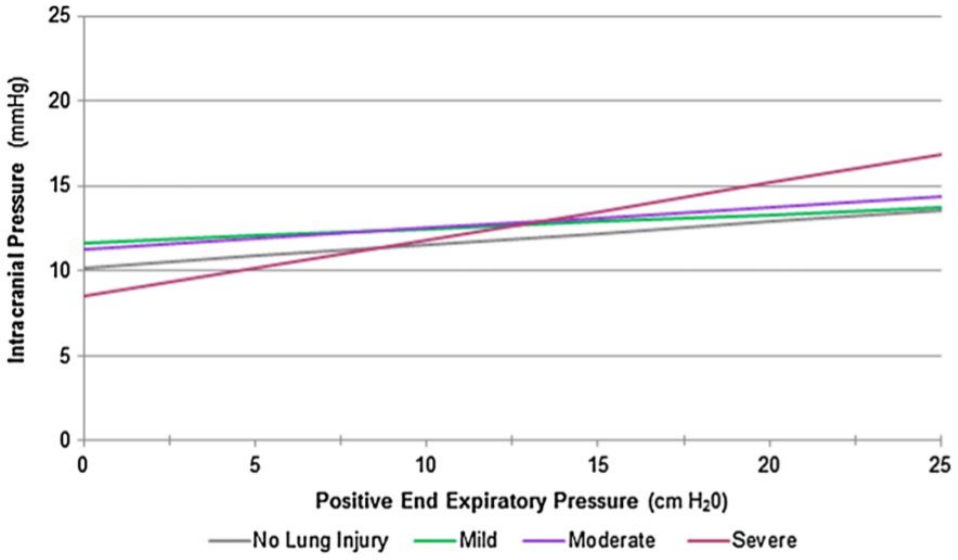
The belief that positive pressure ventilation causes a raised ICP can be traced probably to the article by Apuzzo et al (1977). They investigated this aspect in the dark age of intensive care when everybody was on zero PEEP and with tidal volumes of 1L via horrific steampunk-era ventilators which looked like something from the inside of an early Soviet submarine. Specifically, the authors were using a Bennett MA-1 and a 10cm H_2O PEEP valve. The patients all had severe traumatic brain injury. Apuzzo and colleagues observed that the ICP was increased significantly, such that the CPP was reduced below 60 in several of them. The increase in ICP began abruptly with the initiation of positive pressure, and ended rapidly after the PEEP was withdrawn.



This, of course, was forty years ago. Modern era researchers are supposedly no longer allowed to experiment on human subjects using insane ventilator settings. Muench et al (2005) attempted to answer the question using five healthy female pigs, anaesthetised and monitored with Codman fiberoptic ICP monitors. Where excessive PEEP (20-25 cmH_2O) produced a decrease in cardiac output, the authors used noradrenaline to maintain a normal MAP. To their surprise, Muench et al discovered that there was minimal variation with ICP, CPP and cerebral blood flow in these animals, provided the haemodynamic effects of positive pressure were well-managed. Unsatisfied with five pigs, the authors reproduced these results in twenty humans ventilated for subarachnoid haemorrhage. Only after several days (i.e. when cerebral oedema was well-established and cerebral autoregulation was well-impaired) did the ICP increase in response to PEEP. From an ICP of 10 at a PEEP of 5, the authors saw an increase to an ICP of 20 at PEEP of 20.

This led the authors to conclude that altered cerebral blood flow autoregulation leads patients to become susceptible to the effects of PEEP, whereas normal non-brain-injured patients should remain unaffected. This phenomenon was re-demonstrated by Huseby et al (1981) in dogs, but not by McGuire et al (1997) in human neurosurgical ICU patient, all of who should have had impaired autoregulation, and all of whom had ICPs unaffected by PEEP changes. Similarly, Georgiadis et al (2001) reported that PEEP levels up to 12 cm H_2O had virtually no effect on the ICPs of patients with stroke, except

where it affected their MAP. The authors went so far as to actually measure MCA flow velocities, demonstrating that these patients actually *did* have impaired cerebral blood flow autoregulation. Additionally, in 2017, Boone et al presented data from a massive retrospective study (their graph reproduced below) which demonstrated that ICP rises by 0.31mmHg for every centimeter H2O increase in PEEP in patients with severe lung injury. That means that going from a PEEP of 10 to a PEEP of 15 (potentially game-changig in terms of hypoxia) would produce a trivial 1.5mmHg increase in the ICP.



One might point to the fact that these studies all subjected their patients to relatively mild positive pressure. What might the effects of absurdly high pressures be? Forty years ago, when it was possible to experiment on human subjects using insane ventilator settings, Frost et al (also 1977) subjected brain-injured patients to PEEP as high as 40 cm H_2O for up to 18 hours at a time, with apparently very little effect on the ICP. This is supported by the findings of a more recent article by Nemer et al (2011). These authors performed a comparison of different recruitment manoeuvres for patients with both ARDS and SAH, which saw some of them subjected to a CPAP of 35 cm H_2O for 40 seconds. This resulted in a modest rise of ICP from around 13 to around 20, on average. The pressures used by Bein et al (2001) were even higher – 60 cm H_2O – but the ICP rise in their patients (a mix of ICH and TBI) was only from 13 to 16 mmHg. It must be also pointed out that the *continuous* pressure is the more important parameter. Nemer et al also had patients enrolled in a "pressure controlled recruitment manoeuvre" group, who had a PEEP of 15 and an inspiratory pressure level fo 35 cm H_2O for a few minutes. This group did not

record *any* rise in ICP.

So, to make sense of these data, for exam purposes one might summarise as follows:

- Mechnical ventilation with low to moderate levels of pressure (i.e. with PEEP <15) has little effect on intracranial pressure, particularly in patients without brain injury
- Moderate to high PEEP (15-25) may produce increased ICP in patients with impaired cerebral blood flow autoregulation
- Very high positive airway pressure (PEEP 25-35) reliably produces increased ICP in patients with impaired cerebral blood flow autoregulation.

Effect of positive pressure ventilation on body fluids and electrolytes

Salt and water retention are well-known effects of positive pressure ventilation. This is all the consequence of intrathoracic pressure changes.

The retention of sodium is likely mediated by the atrial natriuretic factor (ANF). Plasma ANF levels dropped by two thirds in a study by Andrivet et al (1988), when patients on zero PEEP were commenced on a PEEP of 12 cm H_2O. The ANF levels returned to normal with the autotransfusion of blood and restoration of normal intrathoracic venous pressure gradients; this was for some reason accomplished not with passive leg raise but with the use of special compressive trousers (it must have been somehow more convenient). Either way, atrial stretch is clearly the main stimulus.

Atrial stretch receptors also mediate the release of vasopressin, which probably mediates the retention of water. Hemmer et al (1980) found that vasopressin secretion by the posterior pituitary increases during positive pressure ventilation- the hormone levels were more than doubled.

Carrying on with the discussion of brutally stupid mechanical effects of ventilation on neurohormonal function, one would not be surprised to discover that by decreasing cardiac output and dropping blood pressure, the application

of positive pressure creates a potent renin-angiotensin-aldosterone response. Frazier et al (1999) summarise the data very well; in summary, there are multiple human and animal studies demonstrating this effect and confirming the relevance of RAAS in its mechanism. Dogs pre-medicated with some ACE-inhibitor retained much less salt and water than unmedicated ones, suggesting that renin and angiotensin-mediated effects are important in this process.

These mechanisms are also responsible for the phenomenon of post-extubation diuresis, a topic explored in Viva 1 (p.2) from the first paper of 2017. Upon withdrawal of positive pressure ventilation, the atria are again stretched by normal venous return. The release of vasopressin is decreased; the release of ANF returns to normal; cardiac output normalises and renin-angiotensin-aldosterone secretion diminishes. Natriuresis and diuresis ensue.

Effect of positive pressure ventilation on renal function

Pannu et al (2004) followed by Koyner & Murray's "Mechanical Ventilation and the Kidney" (2010) are probably the best articles on this topic. Without going into too much detail, it would be fair to summarise the effects of positive pressure ventilation on renal function as "everything worse".

Renal perfusion decreases during positive pressure ventilation. This is due to several factors. A major contribution is probably from the decrease in cardiac output and MAP. Priebe et al (1981) thought that a decrease in intravascular volume was somehow responsible, given that in their anaesthetised dogs the application of PEEP did nothing to impair renal perfusion (as measured by tiny radioactive spheres), even though urine output decreased. However, something different was seen in humans. Annat et al (1983) observed that the 34% decrease in urine output was associated with a reduced GFR (by 19%) and renal blood flow (down by 32%). That this is all related to cardiac output was originally suggested by Qvist et al (1975), who was able to demonstrate a complete reversal of these effects in an animal model where the animals had sufficient volume replacement (in this case, an extra 25ml/kg of blood volume).

Another contribution to the decrease in renal perfusion is the decreased renal perfusion pressure gradient due to venous congestion. The presure in the IVC is reliably low, and may become negative during deep inspiration, which

promotes the efflux of blood from the kidneys. With positive pressure ventilation, the central venous pressure becomes more positive, and renal venous congestion may develop. Shinozaki et al (1988) were able to demonstrate that with a PEEP of 20, the renal venous pressure increased from 4 to 10 mmHg and renal blood flow decreased from 66 to 48 ml/min, of which about 50% was due to the rise in venous pressure.

Effect of positive pressure ventilation on gastrointestinal and hepatic function

Putensen et al (2006) published an excellent overview of these matters, which is unfortunately paywalled; fortunately, Mutlu et al (2001) have one which is just as good but freely available. As for the kidney, the effects of positive pressure ventilation on gastrointestinal function can be summarised as "everything worse and less efficient". In summary, splanchnic perfusion and therefore portal blood flow is decreased, and this appears to be a dose-dependent effect.

Positive pressure ventilation appears to decrease splanchnic blood flow by mechanisms which are somewhat separate from the globally reduced cardiac output which is usually blamed. Bredenberg et al (1983) and Manny et al (1979) were able to demonstrate in dogs that positive pressure ventilation (in these cases, a PEEP of 15) caused a decrease in hepatic arterial blood flow by 48%, whereas the cardiac output was only reduced by 40%. In other words, the application of positive pressure ventilation *redistributed* the blood flow to the viscera. The drop was not particularly large; Putensen et al reaffirm that the application of moderate or even high PEEP should not give rise to clinically significant splanchnic hypoperfusion.

What would be clinically significant effects of this? Presumably, the patients would develop features of gastrointestinal dysfunction associated with hypoperfusion, which would probably range from poor motility, constipation, malabsorption, diarrhoea, ileus, and through to ischaemia ulceration and perforation. Some of this bears a resemblance to reality. Mechanical ventilation seems to be the most important risk factor for stress ulceration according to Cook et al (1994) and Steinberg et al (2002). Gastric perfusion pressures were seen to decrease in ventilated dogs (Fournell et al, 1998) which seems to

support this. Gastric, duodenal and intestinal motility is indeed impaired in a very clinically relevant way: Dive et al (1994) shoved manometers into people and found that motility in these regions was severely impaired, often with complete loss of gastric peristaltic motility.

Effect of positive pressure ventilation on immunology

Pulmonary neutrophil retention, though it sounds quite exotic and weird, is given a short mention in Nunn's (8th ed, P. 470) even while other more important effects of positive pressure ventilation were omitted. In short, this is the effect of leukocytes (being larger and stickier than red blood cells) ending up stuck in the pulmonary vessels which are compressed by positive pressure. There is actual evidence to back this up: Markos et al (1990) sampled blood from the pulmonary arteries and the left ventricle, demonstrating that the white cell count in the pulmonary arterial blood was higher during Valsalva manoeuvres. Similarly, Loick et al (1993) showed that this transpulmonary difference in leukocyte count can occur with even normal PEEP - when they used 10 cm H_2O the transpulmonary difference was increased four-fold (as compared to ZEEP).

Is this pulmonary neutrophilia a bad thing? Nunn's claims this delayed transit of white cells through the pulmonary circulation is intentional, as it allows them time to slow down and marginate into the lung tissue – which seems like a sensible immune defence mechanism. Indeed, Summers et al (2014) were able to show that under normal conditions, inactive neutrophils take only about 14 seconds to cross the pulmonary circulation, whereas activated ones ("primed" neutrophils) were retained in the lung. The lung then de-primes these neutrophils and releases them into the circulation, except in ARDS where these de-priming mechanisms are impaired. Even the normal lung contains a surprisingly large amount of neutrophils - Kuebler & Goetz (2001) estimate that the total pulmonary pool of neutrophils is about 150% of the total circulating number.

Without further digression, one needs to ask: does this seriously have some sort of clinically relevant effect? Would one ever wean the PEEP of a ventilated patient because they genuinely thought that the patient's lungs might

otherwise get dangerously clogged with granulocytes? It is not clear. No literature exists about the impact of this PEEP-induced effect, nor are there any studies trialling interventions which might modify it. In short, it seems like something the exam candidate should know about purely for the purpose of exams.

Probably, the more relevant clinical effect of positive pressure ventilation is the biotrauma which develops as the consequence of ventilator-induced alveolar trauma. That is a much more exciting and important area of discussion, as is produces a systemic inflammatory state associated with worsening organ system failure, thought to be responsible for much of the mortality in ARDS (as few of those patients actually die of hypoxia). However, it would be a stretch to describe this as a consequence of positive pressure ventilation per se. In fact, well managed positive pressure ventilation actually prevents these sorts of outcomes. In any case, the discussion of these matters lends itself more properly to a whole chapter dedicated to open-lung and lung-protective ventilation.

Effect of positive pressure on lymphatic drainage from the lungs

Lung lymphatics are thin (single cell) interstitial conduits which rely on the negative pressure of spontaneous breathing. It would, therefore, make sense that positive pressure ventilation should impede or reverse this process, and therefore inhibit the clearance of foreign materials and toxins from the lung. The pressure in lymphatic vessels, in general, appears to be around 4mmHg, which ends up being higher than the intrathoracic central venous pressure on spontaneous ventilation (which therefore favours the emptying of these sewer-like vessels into the central circulation). Obviously, such a low pressure system will be highly susceptible to even small changes in intrathoracic pressure.

For various reasons anaesthetised animals appear to have borne the brunt of medical violence in research on lymphatic drainage during mechanical ventilation. This is probably because the favoured method of determining lymphatic flow from the lungs is to remove and weigh them. Unfortunately, many of the researchers ended up with wildly different results. Woolverton et

al (1978) used 10 cm H_2O of PEEP in sheep, and found absolutely no difference in lymphatic draianage. Frostell (1987) used oleic acid to induce lung injury in dogs, and found that 10 cm H_2O of PEEP (and mandatory mechanical ventilation) reduced thoracic duct flow by half, whereas spontaneous breathing increased it by 70%. In contrast, Mondejar et al (1996) found that lymphatic drainage of extravascular lung water and thoracic duct flow *increased* with increasing PEEP when the dogs had pulmonary oedema.

Where humans are concerned, what should we believe, and which opinion should the CICM exam candidate regurgitate? As for the latter, one could do worse than borrowing thoughts from Neil Soni (of Berstein & Soni's *Oh's Intensive Care Manual,* you might have heard of him). Soni & Williams (2008) for some reason have an extensive section devoted to lymphatic drainage in their review article on mechanical ventilation. In summary, the authors hold that the pulmonary lymphatics are one one hand filled by positive pressure pushing fluid out of the alveoli and into the interstitium, and on the other hand have their drainage impaired by the increased pressure in the central venous circulation. The net effect is increased lymph production but decreased lymph flow.

This is demonstrated by more cruel animal experiments. Soni and Williams quote a couple of excellent studies which illustrate the point nicely. Haider et al (1987) induced lung injury in mechanically ventilated dogs. The volume of lymph produced by the lung increased, but the flow in the thoracic duct decreased, resulting in some degree of oedema. With the thoracic duct open as a fistula (i.e. lymphatic drainage saved from having to compete with central venous pressure), the lymphatic drainage was revealed as vigorous (it increased fourfold). Also, when their thoracic ducts were open to atmospheric pressure, the dogs' pulmonary oedema rapidly resolved.

Remarkably, Dugernier et al (1989) were able to demonstrate the same phenomenon in humans. Patients with pancreatitis were selected to undergo thoracic duct drainage. *"The duct was exposed through a transverse supraclavicular incision on the left side of the neck and was ligated at the junction with the systemic venous system behind the confluence of the jugular and subclavian veins. ...a 7 F Swan-Ganz catheter was retrogradely inserted into the duct, after cutting off the balloon".* In this manner, lymph was drained from these patients, in a volume ranging from 770ml to 15,600ml over 10 days.

Lung function and chest X-ray appearance improved, which was interpreted as the consequence of improved pulmonary lymphatic drainage. The cynic might point out that a man armed with enough frusemide to produce a negative balance of 15 litres might also have cleared the lungs up nicely, but this would only serve to muddle the discussion.

Previous chapter: Haemodynamic changes during a mechanical breath

Next chapter: Advantages and limitations of non-invasive ventilation

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References

Apuzzo, Michael LJ, et al. "Effect of positive end expiratory pressure ventilation on intracranial pressure in man." Journal of neurosurgery 46.2 (1977): 227-232.

Frost, Elizabeth AM. "Effects of positive end-expiratory pressure on intracranial pressure and compliance in brain-injured patients." Journal of neurosurgery 47.2 (1977): 195-200.

Muench, Elke, et al. "Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation." Critical care medicine 33.10 (2005): 2367-2372.

Huseby, Jon S., et al. "Effects of positive end-expiratory pressure on intracranial pressure in dogs with intracranial hypertension." Journal of neurosurgery 55.5 (1981): 704-707.

McGuire, Glenn, et al. "Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure." Critical care medicine 25.6 (1997): 1059-1062.

Della Torre, Valentina, et al. "Acute respiratory distress syndrome in traumatic brain injury: how do we manage it?." Journal of thoracic disease 9.12 (2017): 5368.

Robba, Chiara, et al. "Effects of prone position and positive end-expiratory pressure on noninvasive estimators of ICP: a pilot study." Journal of neurosurgical anesthesiology 29.3 (2017): 243-250.

Georgiadis, D., et al. "Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke." Stroke 32.9 (2001): 2088-2092.

Nemer, Sérgio N., et al. "Alveolar recruitment maneuver in patients with subarachnoid hemorrhage and acute respiratory distress syndrome: a comparison of 2 approaches." Journal of critical care 26.1 (2011): 22-27.

Bein, T., et al. "Lung recruitment maneuver in patients with cerebral injury: effects on intracranial pressure and cerebral metabolism." Intensive care medicine 28.5 (2002): 554-558.

Koyner, Jay L., and Patrick T. Murray. "Mechanical ventilation and the kidney." Blood purification 29.1 (2010): 52-68.

Hemmer, Margaret, et al. "Urinary antidiuretic hormone excretion during mechanical ventilation and weaning in man." Anesthesiology 52.5 (1980): 395-400.

Andrivet, P., et al. "Involvement of ANF in the acute antidiuresis during PEEP ventilation." Journal of Applied Physiology 65.5 (1988): 1967-1974.

Burchardi, Hilmar. "Effects of mechanical ventilation on kidney function." Critical Care Nephrology. Springer, Dordrecht, 1998. 1055-1065.

Frazier, Susan K. "Neurohormonal responses during positive pressure mechanical ventilation." Heart & Lung: The Journal of Acute and Critical Care 28.3 (1999): 149-167.

Annat, G., et al. "Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins." Anesthesiology 58.2 (1983): 136-141.

Pannu, Neesh, and Ravindra L. Mehta. "Effect of mechanical ventilation on the kidney." Best Practice & Research Clinical Anaesthesiology 18.1 (2004): 189-203.

Priebe, HANS-JOACHIM, JOEL C. Heimann, and J. O. H. N. Hedley-Whyte. "Mechanisms of renal dysfunction during positive end-expiratory pressure ventilation." Journal of Applied Physiology 50.3 (1981): 643-649.

Annat, G., et al. "Effect of PEEP ventilation on renal function, plasma renin, aldosterone, neurophysins and urinary ADH, and prostaglandins." Anesthesiology 58.2 (1983): 136-141.

Qvist, J., et al. "Hemodynamic responses to mechanical ventilation with PEEP: the effect of hypervolemia." Anesthesiology 42.1 (1975): 45-55.

Shinozaki, Masahiro, et al. "Hemodynamic relationship between renal venous pressure and blood flow regulation during positive end-expiratory pressure." Critical care medicine 16.2 (1988): 144-147.

Bredenberg, Carl E., and Andrew M. Paskanik. "Relation of portal hemodynamics to cardiac output during mechanical ventilation with PEEP." Annals of surgery 198.2 (1983): 218.

Manny, Jonah, Richard Justice, and Herbert B. Hechtman. "Abnormalities in organ blood flow and its distribution during positive end-expiratory pressure." Surgery 85.4 (1979): 425-432.

Fournell, A., T. W. L. Scheeren, and L. A. Schwarte. "PEEP decreases oxygenation of the intestinal mucosa despite normalization of cardiac output." Oxygen Transport to Tissue XX. Springer, Boston, MA, 1998. 435-440.

Mutlu, Ece A., and Phillip Factor. "GI complications in patients receiving mechanical ventilation." Chest 119.4 (2001): 1222-1241.

Dive, Alain, et al. "Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study." Critical care medicine 22.3 (1994): 441-447.

Markos, J., et al. "Effect of raised alveolar pressure on leukocyte retention in the human lung." Journal of Applied Physiology 69.1 (1990): 214-221.

Loick, H. M., et al. "Ventilation with positive end-expiratory airway

pressure causes leukocyte retention in human lung." Journal of Applied Physiology 75.1 (1993): 301-306.

Summers, Charlotte, et al. "Pulmonary retention of primed neutrophils: a novel protective host response, which is impaired in the acute respiratory distress syndrome." Thorax (2014): thoraxjnl-2013.

Kuebler, Wolfgang M., and Alwin E. Goetz. "The marginated pool." European surgical research 34.1-2 (2002): 92-100.

Mondejar, Enrique Fernandez, et al. "Ventilation with positive end-expiratory pressure reduces extravascular lung water and increases lymphatic flow in hydrostatic pulmonary edema." Critical care medicine 24.9 (1996): 1562-1567.

Frostell, C., et al. "Thoracic and abdominal lymph drainage in relation to mechanical ventilation and PEEP." Acta anaesthesiologica scandinavica 31.5 (1987): 405-412.

Woolverton, William C., Kenneth L. Brigham, and Norman C. Staub. "Effect of positive pressure breathing on lung lymph flow and water content in sheep." Circ Res 42.4 (1978): 550-557.

Soni, N., and P. Williams. "Positive pressure ventilation: what is the real cost?." British journal of anaesthesia 101.4 (2008): 446-457.

Haider, M., H. Schad, and N. Mendler. "Thoracic duct lymph and PEEP studies in anaesthetized dogs. I. Lymph formation and the effect of a thoracic duct fistula on lymph flow." Intensive care medicine 13.3 (1987): 183-191.

Dugernier, T. H., et al. "Prospective evaluation of thracic-duct drainage in the treatment of respiratory failure complicating severe acute pancreatitis." Intensive care medicine 15.6 (1989): 372-378.

Boone, Myles D., et al. "The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics." *Neurocritical care* 26.2 (2017): 174-181.

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